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Accelerated Dose Escalation with 3 Injections of an Aluminum Hydroxide-Adsorbed Allergoid Preparation of 6 Grasses Is Safe for Children and Adolescents with Moderate to Severe Allergic Rhinitis

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Keywords
Allergen-specific immunotherapy · Allergic rhinitis · Children · Cytokines · Nasal allergy tolerance/suppression

Abstract
A high-dose, accelerated escalation schedule during subcutaneous allergen-specific immunotherapy (AIT) is safe and well-tolerated in adults. However, there are no data in children and adolescents. The aim of the present trial was to assess safety and tolerability of an accelerated dose escalation schedule of an AIT with a grass pollen allergoid in children and adolescents with moderate to severe seasonal rhinoconjunctivitis in a multicenter, open-label, randomized phase II trial. The dose escalation scheme for patients in the One Strength Group included 3 injections with 1 strength B (10,000 TU/mL), whereas the dose escalation scheme for the Standard group included 7 injections with 2 strengths A (1,000 TU/mL) and B (10,000 TU/mL) of an allergoid grass pollen preparation. Overall, n = 50 children (n = 25 in each group; mean age 8.9 + 1.54 years) and n = 37 adolescents (n = 20 and n = 17; 14.2 + 1.62 years) were randomized. For all patients, the mean treatment duration was 59.4 days in the One Strength group and 88.6 days in the Standard group. Treatment-emergent adverse events (TEAEs) related to AIT were reported in 52 and 40% in children and 35 and 35.3% in adolescents, respectively. Systemic allergic reactions occurred in about 5% of our patients and were reported in more patients of the One Strength group (6.7 vs. 2.4%). All systemic reactions were classified as WAO Grade 1. Accelerated high-dose escalation with an aluminum hydroxide-adsorbed grass pollen allergoid can be initiated with a safety and tolerability profile comparable to the standard dose escalation schedule in children and adolescents with allergic rhinitis with or without asthma.

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Introduction

Allergen-specific immunotherapy (AIT) is the spearhead of our limited arsenal of sustainable treatment options fighting the epidemic of allergic diseases [1]. For allergic rhinitis (AR) and/or allergic asthma, sublingual and subcutaneous administration of AIT has been shown to be efficacious and saves treatment options. However, the acceptance and adherence of subcutaneous AIT is limited by long-term updosing and maintenance phases [2]. During the last years, a number of clinical trials became available demonstrating that accelerated high-dose escalation schedules can be applied in patients with AR with or without asthma with a comparable safety and tolerability profile as the standard escalation schedules. Recently, Chaker et al. [3] have demonstrated that an accelerated 4-dose escalation scheme of a grass pollen allergoid starting with 200 therapeutic units (TU) can be given with a beneficial safety profile comparable to the standard 7-dose escalation regime starting with 100 TU. Taking a step forward, we were able to demonstrate that also an accelerated high-dose escalation schedule of a grass pollen allergoid starting with a 5 times higher initial dose (1,000 TU) can be safely administered. Eighty percent of the patients in the high-dose escalation group reached the first AIT injection of the maintenance phase without dose adjustment [4]. While a slightly higher number of patients in the high-dose escalation group reported systemic allergic reactions (n = 4; 8.9%) compared to the standard dose escalation group (n = 1; 2.4%), all systemic allergic symptoms were classified as mild (WAO Grade 1 or Grade 2). However, all these observations are limited to adult populations and data in the pediatric and adolescent subgroups are sparse. Therefore, we performed a multicenter, open-label, randomized phase II clinical trial in pediatric patients with rhinitis or rhinoconjunctivitis caused by grass pollen sensitization and applied two different updosing regimes of a grass pollen allergoid.

Methods

Patients

This multicenter, open-label, randomized, parallel, active-controlled phase II trial was conducted in pediatric patients (5 to <18 years of age) with rhinitis or rhinoconjunctivitis caused by grass pollen. Patients between 5 and <18 years of age with the diagnosis of immunoglobulin E (IgE)-mediated seasonal moderate to severe AR according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline [5] or rhinoconjunctivitis with or without allergic asthma caused by grass pollen could be enrolled after providing informed consent. Further inclusion criteria included a positive skin prick test (≥3 mm in diameter) and specific IgE (≥0.70 kU/L) against grass pollen. In addition, patients had to experience AR or rhinoconjunctivitis symptoms triggered by grass pollen exposure for at least 1 month in the period from May to August, and they had to receive previous antiallergic treatment for at least two seasons prior to enrollment. In cases with a diagnosis of asthma, the asthma had to be diagnosed and classified as "well-controlled" according to the Global Initiative for Asthma (GINA) guideline [6]. Exclusion criteria included prior history of confirmed anaphylaxis after an AIT injection with grass pollen within the last 5 years, current treatment with any kind of immunotherapy, and uncontrolled/partly controlled asthma according to the Global Initiative for Asthma (GINA) guideline. Moreover, patients with autoimmune diseases, β-blocker use, and contraindication for the use of adrenalin could not be enrolled.

Patients were randomized into a group with accelerated dose escalation (Group I or "One Strength group") and a group with standard dose escalation (Group II or "Standard group") in a 1:1 ratio within each site. In order to achieve a balanced distribution of patients within each treatment group according to the two different age-groups (5 to <12 years and 12 to <18 years), patients were stratified according to their age.

The trial was conducted in autumn and winter, that is, prior to the grass pollen season. All patients were recruited between October 2018 and March 2019. No placebo group was included in this trial (EudraCT 2018-000548-25).

Trial Design and Treatment

This was a multicenter, open-label, randomized, parallel, active-controlled phase II trial in pediatric patients with rhinitis or rhinoconjunctivitis caused by grass pollen. It was conducted in Germany, Poland, Russia, and Spain.

The grass pollen allergoid (Allergovit® 6-grasses; Allergopharma GmbH and Co. KG, Reinbek, Germany) contains a mixture of allergens from 6 grass pollen species (*Holcus lanatus, Dactylis glomerata, Lolium perenne, Phleum pratense, Poa pratensis,* and *Festuca pratensis*). The allergoid is coprecipitated with aluminum hydroxide. The preparation is provided in two strengths: A (1,000 TU/mL) and B (10,000 TU/mL). The approximate estimation of major allergen content for *Phleum pratense* (Phl p 5) is 25 µg equivalent/mL in Allergovit® 6-grasses (in strength 10,000 TU) [7].

The One Strength group received 3 injections of one strength (B) of the grass pollen allergoid (0.1 mL of 1,000 TU, 0.3 mL of 3,000 TU, and 0.6 mL of 6,000 TU) at weekly intervals. The Standard group started with 1/10 of the dose of the One Strength group and received 7 injections (strength A: 0.1 mL of 100 TU, 0.2 mL of 200 TU, 0.4 mL of 400 TU, and 0.8 mL of 800 TU; strength B: 0.15 mL of 1,500 TU, 0.3 mL of 3,000 TU, and 0.6 mL of 6,000 TU). When the maintenance dose had been reached, both groups received 2 maximum-dose injections (0.6 mL of 6,000 TU) of strength B after 14 and 28 days. After each injection, patients in both groups were supervised for at least 120 min to monitor potential adverse reactions. Dosage modification was performed if local and/or systemic adverse events (AEs) occurred, based on a predefined regime. The WAO grading system was used to decide on dose modification in case of an systemic reaction. Briefly, if the patient experienced a systemic allergic reaction of any WAO grade following the first injection or a WAO Grade 3 or 4 reaction, then the patient must be discontinued from the trial. A WAO Grade 1 reaction resulted in a reduction by 1 dose step of the last applied

dose; a WAO Grade 2 resulted in a reduction by 2 dose steps of the last applied dose. If the first dose reduction was not tolerated in case of a WAO Grade 1 or 2 reaction, a second dose reduction by 1 dose step of the last applied dose was administered. No more than 2 dose reductions per patient due to an AE were tolerated during the trial.

Assessment of AR and Asthma

To assess the severity of the patient's AR, the symptomatic history according to the Allergic Rhinitis and its Impact on Asthma (ARIA) guideline was documented by the investigator at the screening visit. Peak flow measurements were also performed. The asthma status of all patients was monitored by the Asthma Control Questionnaire.

Assessment of Safety and Tolerability End Points

Safety and tolerability end points focused on treatment-emergent AEs (TEAEs), defined as any AE that started or worsened after the first intake of trial medication until 30 days after the last administration of the investigational medicinal product (IMP) or trial-related procedure. An adverse drug reaction was defined as all untoward and unintended responses to the IMP related to any dose administered. A local adverse reaction was defined as an AE related or not related to the IMP and occurring at the injection site. A systemic allergic reaction was defined as an AE related or not related to the IMP and graded as systemic according to the WAO grading system based on the organ systems involved and the severity of the reaction.

Apart from AE data, changes in laboratory values (hematology, clinical chemistry, and urinalysis) measured before and after the treatment phase, changes in vital signs and lung function measured before and after the treatment phase, and the assessment of overall tolerability, by the investigator and the patient, using a 5-point Likert scale (1 = very bad; 5 = very good) were documented. The trial was supervised by an independent Data and Safety Monitoring Board.

Statistical Analysis

Due to the exploratory design of the trial, there was no formal estimation of sample size. It was planned to randomize 35 patients per age and treatment group, which equals a total of 140 patients (children/adolescents and group I [One Strength]/group II [Standard]), to guarantee a probability of 95% that AEs with a true incidence rate of 8.6% occur at least once in the respective treatment group [8].

The patients were assigned to the following sets before starting the analysis: the "All-Patients Set" comprised patients that gave their informed consent. For this group, the patients' disposition and reasons for premature trial termination are described. The "Safety Set" (SAF) was the group of patients who received at least 1 dose of trial medication. It is the basic analysis set for all assessments of safety and tolerability. For this set, exposure to IMP was analyzed.

Numbers and incidence rates of AEs and severe AEs with causal relationship to the IMP are reported separately for both age-groups. Statistical tests (Fisher's exact test, χ^2 test, and Wilcoxon-Mann-Whitney U test) were performed when adequate. Otherwise, the analysis was performed descriptively and explained by comparing events and frequencies between groups. For all statistical tests, a significance level of $\alpha = 5\%$ was chosen.

Results

Patients

A total of 115 patients (children and adolescents) were enrolled in this trial, 60 children and 55 adolescents. Of the 60 screened children, 50 were randomized (safety set), 25 patients to the One Strength group and 25 patients to the Standard group (Fig. 1). A total of 3 randomized pediatric patients prematurely discontinued the trial, 1 in the One Strength group (AE: injection site swelling) and 2 in the standard group (AE: varicella and other reasons). In total, 37 adolescent patients were randomized, 20 patients to the One Strength group and 17 patients to the Standard group (Fig. 1). Two adolescent patients prematurely discontinued the trial, 1 in the One Strength group (AE: urticaria) and 1 in the Standard group (personal reasons).

For both children and adolescents, demographic characteristics were generally comparable between groups (Table 1). The incidence of patients' allergy-specific history was generally comparable between groups. Almost all pediatric patients experienced nasal (98.0%) and ocular symptoms (86.0%). Wheezing, shortness of breath, and cough was reported for nearly half of the patients (ranged from 40.0 to 46.0%); chest tightness was reported for 32.0% of the pediatric patients (see online suppl. Table 1; see www.karger.com/doi/10.1159/000512561 for all online suppl. material). The mean and median duration of symptoms was generally comparable between the groups. All adolescent patients experienced nasal symptoms, and the majority of patients experienced ocular symptoms (78.4%). Wheezing, shortness of breath, and cough was reported for about one-sixth of the patients (ranged from 16.2 to 18.9%); chest tightness was reported for 13.5% of the adolescent patients. The incidence of patients' allergy-specific history was generally comparable between groups; incidence in wheeze (25.0 vs. 11.8%), shortness of breath (30.0 vs. 5.9%), and chest tightness (20.0 vs. 5.9%) was higher in the One Strength group than in the Standard group.

For both children and adolescents, immunological profiles (total and specific IgE, i.e., mugwort, rye, birch, *P. pratense*, grass mix/early bloom, *D. farinae*, and *D. pteronyssinus*) did not differ significantly between treatment groups at baseline (Table 1). In the One Strength group, the majority of patients received 5 injections in total (children: 92.0%; adolescents: 85.0%) and in the standard group, 9 injections (children: 80.0%; adolescents: 94.1%). Accordingly, the median treatment duration was shorter in the One Strength group compared to

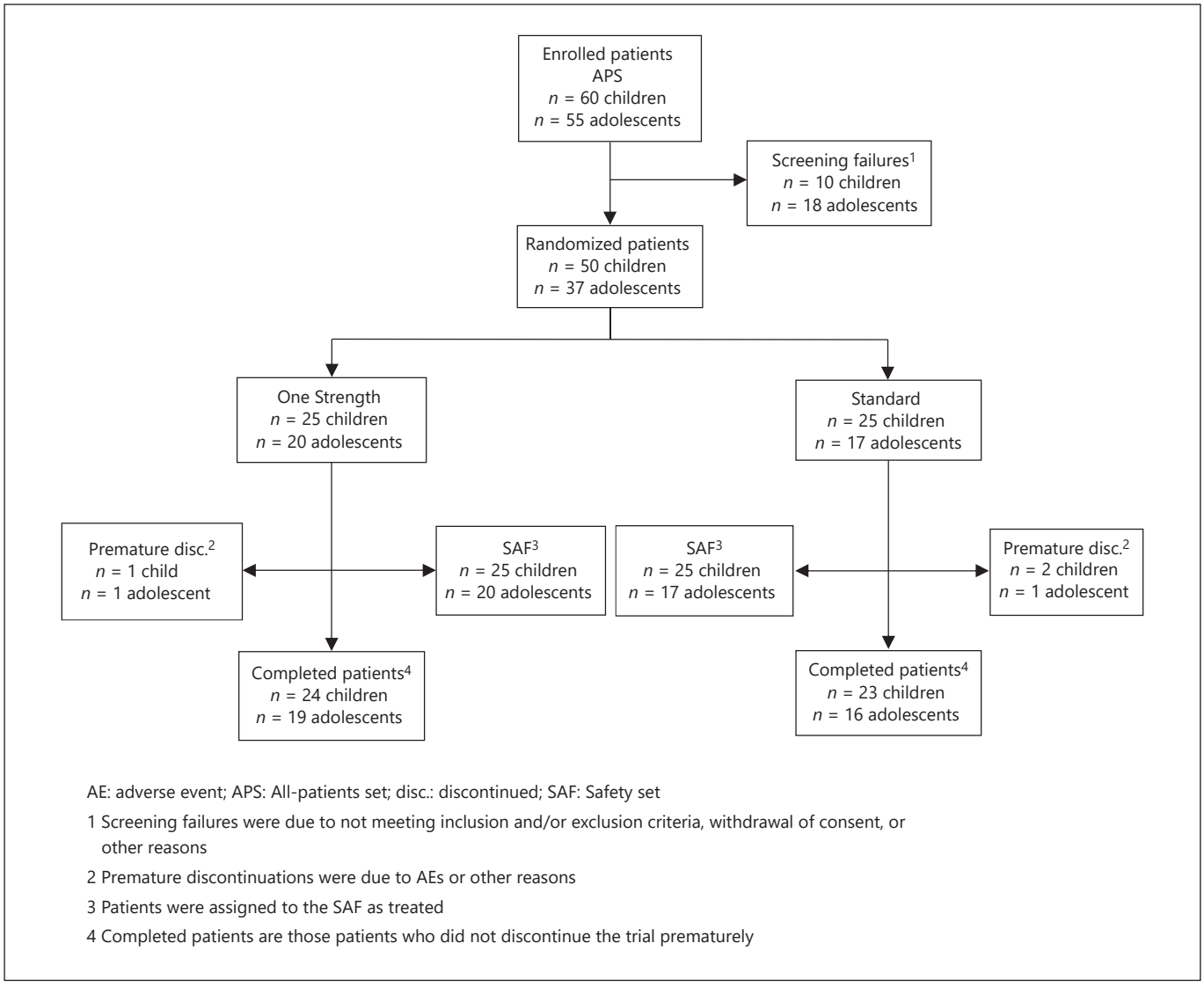

Fig. 1. Disposition of patients. AE, adverse event; APS, all-patients set; Disc., discontinued; SAF, safety set.

that in the Standard group for children (One Strength group: 61 days; Standard group: 87 days) and adolescents (One Strength group: 61 days; Standard group: 85 days). Median compliance was 100% for children and adolescents in both treatment groups.

Adverse Events

Overall, $n = 51$ (58.6%) patients reported at least 1 TEAE. The proportion of patients with at least 1 TEAE during the trial was similar in both groups (One Strength group: 60.0%; Standard group: 57.1%).

In the subgroup of children, $n = 34$ (68.0%) patients reported at least one TEAE (Table 2). The proportion of pediatric patients with at least one TEAE during the trial was slightly higher in the One Strength group than in the Standard group (72.0 vs. 64.0%; $p = 0.7624$). In the subgroup of adolescents, 17 (45.9%) patients reported at least one TEAE. The proportion of adolescent patients with at least one TEAE during the trial was similar between groups (One Strength group: 45.0%; Standard group: 47.1%; $p = 1.0000$; Table 2).

Table 1. Demographic data and baseline characteristics: SAF

	Children		Adolescents	
	One Strength *n* = 25	Standard *n* = 25	One Strength *n* = 20	Standard *n* = 17
Age, years				
Mean (SD)	8.9 (1.76)	8.9 (1.32)	13.9 (1.41)	14.6 (1.80)
Median	9.0	9.0	14.0	15.0
Min.–max.	5–11	6–11	12–16	12–17
Gender, *n* (%)				
Male	15 (60.0)	17 (68.0)	14 (70.0)	9 (52.9)
Female	10 (40.0)	8 (32.0)	6 (30.0)	8 (47.1)
Asthma (yes), *n* (%)	15 (60.0)	14 (56.0)	5 (25.0)	3 (17.6)
Among them, *n* (%)				
Inhaled steroids (yes)	13 (86.7)	10 (71.4)	3 (60.0)	3 (100)
Inhaled steroids (no)	2 (13.3)	4 (28.6)	2 (40.0)	0
Ethnicity, *n* (%)				
White	25 (100)	25 (100)	20 (100)	17 (100)
BMI, kg/m^2				
Mean (SD)	17.7 (2.46)	18.3 (3.95)	20.0 (3.24)	20.6 (3.35)
Median	17.5	17.1	19.5	20.0
Min.–max.	13–22	13–29	15–29	17–29
Pet contact, *n* (%)				
No	20 (80.0)	19 (76.0)	14 (70.0)	11 (64.7)
Intermittent	3 (12.0)	0	0	0
Permanent	2 (8.0)	6 (24.0)	6 (30.0)	6 (35.3)
Total IgE, kU/L				
Median	352.00	428.00	262.50	220.00
Min.–max.	16.2–845.0	55.0–3,615.0	37.8–6,734.0	58.6–3,113.0
Specific IgE, kU/L for grass mix/early bloom				
Median	32.500	45.600	16.300	27.500
Min.–max.	1.39–100.00	0.76–100.00	0.71–100.00	1.30–100.00
Specific IgG4 for *Phleum pratense*, mg/L				
Median	0.240	0.340	0.250	0.330
Min.–max.	0.07–1.79	0.07–6.28	0.07–0.93	0.07–1.57

N, number of patients; *n* (%), number (percentage) of patients with data; SAF, safety set.

Table 2. Overview of TEAEs

	Children				Adolescents			
	One Strength *n* = 25		Standard *n* = 25		One Strength *n* = 20		Standard *n* = 17	
	n (%)	e	*n* (%)	e	*n* (%)	e	*n* (%)	e
TEAEs	18 (72.0)	59	16 (64.0)	58	9 (45.0)	55	8 (47.1)	43
TEAEs related to IMP	13 (52.0)	21	10 (40.0)	27	7 (35.0)	39	6 (35.3)	32
Local reactions	10 (40.0)	16	10 (40.0)	27	6 (30.0)	36	5 (29.4)	25
Systemic allergic reactions	2 (8.0)	2	0	0	1 (5.0)	1	1 (5.9)	5
Other type of events	14 (56.0)	41	10 (40.0)	31	6 (30.0)	18	5 (29.4)	13
TEAEs leading to discontinuation	1 (4.0)	3	1 (4.0)	1	1 (5.0)	1	0	0
Treatment-emergent SAE	0	0	0	0	1 (5.0)	1	1 (5.9)	5
Treatment-emergent SAE related to IMP	0	0	0	0	1 (5.0)	1	1 (5.9)	5

e, number of events (TEAEs); IMP, investigational medicinal product; *n*, number of patients; *n* (%), number (percentage) of patients with at least one TEAE; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

Table 3. TEAEs related to IMP and intensity of TEAEs

	Children				Adolescents			
	One Strength $n = 25$		Standard $n = 25$		One Strength $n = 20$		Standard $n = 17$	
	n (%)	e	*n* (%)	e	*n* (%)	e	*n* (%)	e
Overall	13 (52.0)	21	10 (40.0)	27	7 (35.0)	39	6 (35.3)	32
Mild		18		25		27		29
Moderate		3		2		12		3
Severe		0		0		0		0
General disorders and administration site conditions	10 (40.0)	17	10 (40.0)	27	6 (30.0)	36	5 (29.4)	25
Injection site swelling	8 (32.0)	11	8 (32.0)	11	5 (25.0)	13	4 (23.5)	10
Injection site erythema	2 (8.0)	3	3 (12.0)	11	3 (15.0)	11	3 (17.6)	7
Injection site pruritus	2 (8.0)	2	3 (12.0)	3	4 (20.0)	8	2 (11.8)	8
Injection site edema	0	0	1 (4.0)	1	0	0	0	0
Injection site pain	0	0	1 (4.0)	1	3 (15.0)	3	0	0
Swelling	1 (4.0)	1	0	0	0	0	0	0
Injection site discomfort	0	0	0	0	1 (5.0)	1	0	0
Investigations	1 (4.0)	1	0	0	0	0	0	0
Forced expiratory volume decreased	1 (4.0)	1	0	0	0	0	0	0
Musculoskeletal and connective tissue disorders	1 (4.0)	1	0	0	0	0	0	0
Pain in extremity	1 (4.0)	1	0	0	0	0	0	0
Nervous system disorders	1 (4.0)	1	0	0	0	0	1 (5.9)	2
Headache	1 (4.0)	1	0	0	0	0	1 (5.9)	1
Somnolence	0	0	0	0	0	0	1 (5.9)	1
Respiratory, thoracic and mediastinal disorders	0	0	0	0	2 (10.0)	2	1 (5.9)	1
Cough	0	0	0	0	0	0	1 (5.9)	1
Rhinitis, allergic	0	0	0	0	1 (5.0)	1	0	0
Sneezing	0	0	0	0	1 (5.0)	1	0	0
Skin and subcutaneous tissue disorders	1 (4.0)	1	0	0	1 (5.0)	1	1 (5.9)	2
Dermatitis, allergic	1 (4.0)	1	0	0	0	0	0	0
Urticaria	0	0	0	0	1 (5.0)	1	1 (5.9)	1
Pruritus	0	0	0	0	0	0	1 (5.9)	1
Eye disorders	0	0	0	0	0	0	1 (5.9)	1
Conjunctival edema	0	0	0	0	0	0	1 (5.9)	1
Infections and infestations	0	0	0	0	0	0	1 (5.9)	1
Rhinitis	0	0	0	0	0	0	1 (5.9)	1

e, number of events (TEAEs); IMP, investigational medicinal product; *n*, number of patients; *n* (%), number (percentage) of patients with at least one TEAE; PT, preferred term; SAF, safety set; SOC, system organ class; TEAE, treatment-emergent adverse event.

In the subgroup of children, of the 117 reported TEAEs, 48 TEAEs were assessed as related to IMP by the investigators and occurred in 23 (46.0%) patients. Slightly more pediatric patients experienced at least one IMP-related TEAE in the One Strength group than in the Standard group (52.0 vs. 40.0%; $p = 0.5709$) with slightly smaller absolute and relative number of events in the One Strength group than in the Standard group (21 vs. 27, ratio of TEAE per patient: 1.6 vs. 2.7). In the subgroup of adolescents, of the 98 reported TEAEs, 71 TEAEs were assessed as related to IMP by the investigators and occurred in 13 (35.1%) patients. The number of adolescent patients who experienced at least one IMP-related TEAE was comparable between groups (One Strength group: 35.0%; Standard group: 35.3%; $p = 1.0000$) with slightly more events in the One Strength group than in the Standard group (39 vs. 32, ratio of TEAE per patient 5.6 vs. 5.3). An overview of TEAEs related to the IMP is presented in Table 3 for the subgroup of children and adolescents.

For both children and adolescents, most of the reported TEAEs related to IMP were local reactions: 105 local reactions were reported with an equal distribution in both groups (One Strength group: 53 TEAEs; Standard group: 52 TEAEs). The number of affected patients was similar between both groups (One Strength group: 35.6%; Standard group: 35.7%; $p = 1.0$).

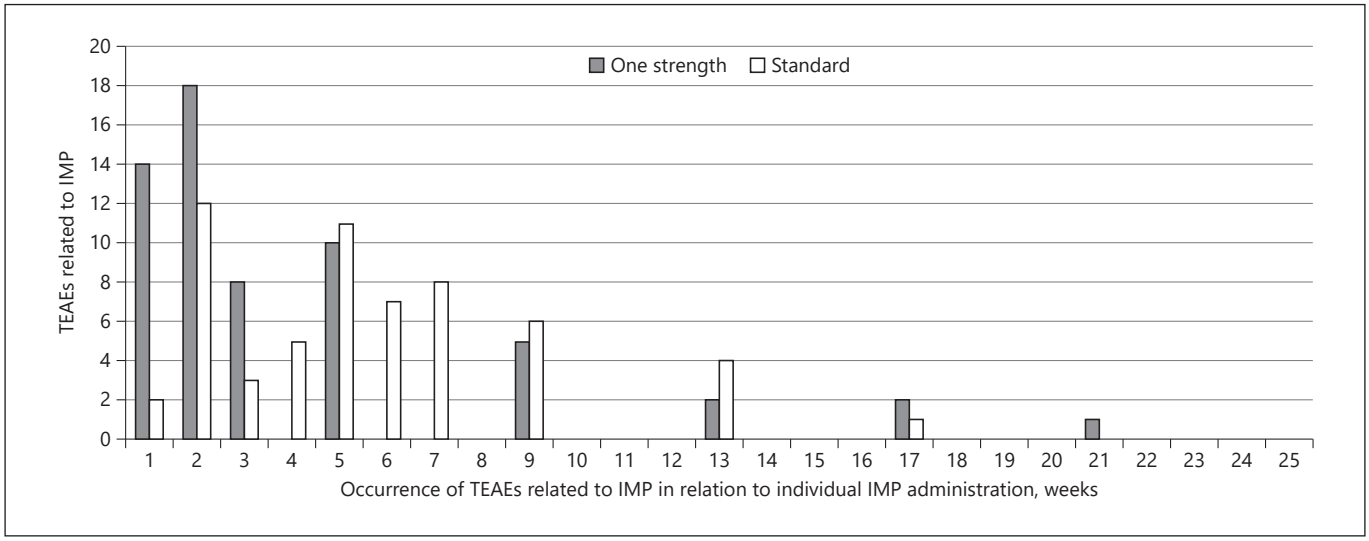

Fig. 2. TEAEs related to IMP in relation to individual injections – pooled analysis (children, adolescents, and adults). IMP, investigational medicinal product; TEAE, treatment-emergent adverse event.

In the subgroup of children, 44 local reactions related to IMP occurred slightly less frequently in the One Strength group than in the Standard group (17 vs. 27 TEAEs). The number of affected patients was equal in both groups (One Strength group: 40.0%; Standard group: 40.0%; $p = 1.0$). In the subgroup of adolescents, 61 local reactions related to IMP occurred slightly more frequently in the One Strength group than in the Standard group (36 vs. 25 TEAEs). The number of affected patients was similar between both groups (One Strength group: 30.0%; Standard group: 29.4%; $p = 1.0$).

No deaths and no suspected unexpected serious adverse reactions were reported during the trial. Only in the subgroup of adolescents, serious AEs occurred in 1 patient of the One Strength group and another patient of the Standard group. Overall, 3 patients experienced TEAEs leading to premature discontinuation from the trial (One Strength group: 2 patients, Standard group: 1 patient). One adolescent in the One Strength group suffered from a systemic allergic reaction (urticaria) which was related to study medication. One child in the One Strength group suffered from non-serious adverse drug reactions (injection site swelling, swelling, and pain) which were related to study medication. Another child in the Standard group suffered from a non-serious AE (varicella) which was not related to study medication. All these patients were included in final computation.

Systemic Adverse Reactions

Overall, systemic allergic reactions occurred in 4 (4.6%) patients, 3 (6.7%) patients in the One Strength group and 1 (2.4%) in the Standard group ($p = 0.6171$). In the subgroup of children, 2 systemic allergic reactions related to IMP occurred in 2 patients, all of which were reported in the One Strength group: forced expiratory volume decreased and allergic dermatitis. There was no statistically significant difference between groups ($p = 0.49$). Both systemic allergic reactions in pediatric patients were assessed as non-serious.

In the subgroup of adolescents, 6 systemic allergic reactions related to IMP occurred in 2 patients. Of the 6 reported events, 1 (urticaria) occurred in 1 patient of the One Strength group, and 5 systemic TEAEs were reported from 1 patient of the Standard group. The allergic reactions were conjunctival edema, cough, pruritus, rhinitis, and urticaria. There was no statistically significant difference between groups. All 6 systemic allergic reactions in adolescent patients were assessed as serious.

Time to Onset of TEAEs Related to IMP

Overall, most of the TEAEs related to IMP were reported during these escalation phases. For both children and adolescents in the One Strength group, most IMP-related TEAEs occurred after the second IMP administration with a decrease in the number of IMP-related TEAEs with further IMP injections (Fig. 2). In contrast, for children and adolescents in the Standard group, the number

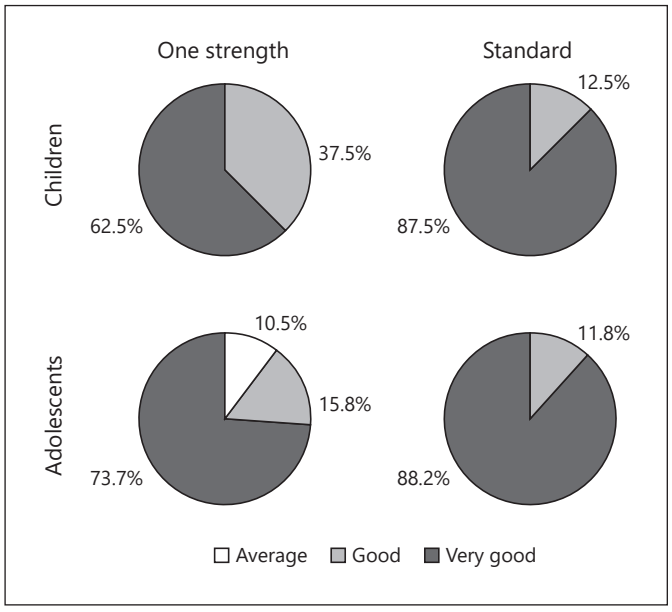

Fig. 3. Assessment of overall tolerability in the two groups by the investigator after the last dose of the escalation phase on a 5-point Likert scale (very bad – bad – average – good – very good).

of IMP-related TEAEs after the first and second IMP doses was lower compared to the One Strength group; here, the peak of IMP-related TEAEs occurred between the fifth and seventh IMP injection.

For both children and adolescents, most of the IMP-related TEAEs occurred up to 6 h after IMP administration (children: 30 of 48 TEAEs; adolescents: 48 of 71 TEAEs). In the subgroup of children, a slightly fewer number occurred in the One Strength group than in the Standard group (12 TEAEs vs. 18 TEAEs). In the subgroup of adolescents, a slightly higher number occurred in the One Strength group than in the Standard group (28 TEAEs vs. 20 TEAEs). In children and in adolescents, after 6 h, the number of TEAEs decreased continuously. Further analyses suggest that there was no influence of the reaction type (local reaction or systemic allergic reaction) on the time to onset, neither in children nor in adolescents. A more detailed analysis of the onset period >30 min to ≤6 h in both populations revealed that the majority of TEAEs related to IMP occurred up to 2 h (children) and 3 h (adolescents), respectively, after IMP injection.

Tolerability and Other Safety Parameters

All investigators (children) and the majority of investigators (adolescents), respectively, assessed the overall tolerability at the end of the escalation phase as "very good" or "good" (children: 75.0 and 25.0%; adolescents: 80.6 and 13.9%, Fig. 3). Similar results were obtained for the patient's assessment (children: 87.5 and 12.5%; adolescents: 80.6 and 16.7%). The investigators judged the tolerability for children in the One Strength group after the last dose of the escalation phase slightly inferior to the Standard group (very good: 62.5 vs. 87.5%). This difference was statistically significant ($p = 0.0494$). All other assessment results were similar for both the One Strength group and the Standard group ($p > 0.05$). Furthermore, the investigators' and patients' assessments at the final visit revealed similar results.

For all patients (children and adolescents), there were no notable differences between the asthmatic and non-asthmatic patients. Furthermore, there were no clinically relevant differences between the treatment groups in terms of changes in clinical chemistry, hematology, and urinalysis values during the trial. The immunological profile was assessed at baseline and at the final visit. During the course of the trial, the mean amount of IgG4 against Timothy grass pollen increased notably over time in both treatment groups for children and adolescents ($p < 0.0001$). The comparison of the mean changes from baseline revealed no notable difference between treatment groups at final visit for children and adolescents ($p > 0.05$).

Discussion

Administration of grass pollen allergoid preparations using the standard dose escalation scheme is an efficacious and safe treatment option in children and adolescents with AR and/or allergic asthma [9]. The use of alternative dose escalation schemes with fewer injections is increasingly common in daily practice. Since reported reactions were mainly local and mild of intensity, the use of an accelerated dose escalation should be expected to be safe and comparable to standard schemes with regard to the appearance, frequencies, and severity of side effects [10]. However, up to now, there are only limited data about side effects of shortened escalation schemes with higher injection doses in children and adolescents. In this open-label, randomized, active-controlled trial, we were able to demonstrate that an accelerated high-dose escalation schedule using 3 injections of a grass pollen allergoid can be applied with a comparable safety profile as the standard escalation schedule using 7 injections. Nearly 90% of all randomized patients reached the first AIT injection of the maintenance phase without dose adjust-

ment. Moreover, the overall tolerability at the end of the escalation phase was assessed as "very good" or good" by the majority of investigators and patients. Altogether, our results point toward a favorable safety profile of the accelerated updosing scheme.

For all patients, children, and adolescents, most of the reported TEAEs related to AIT were local reactions with an equal distribution in both groups. Local reactions from AIT are common during the updosing and maintenance phase [11]. In our study, not only the absolute number of TEAS but also the number of affected patients was similar between both groups. Overall, the most commonly reported local reactions related to AIT were injection site swelling, followed by injection site erythema and injection site pruritus. These data fit precisely with the results of our recently published clinical trial in adults [4]. However, all local symptoms were reported more frequently in adults compared to children and adolescents. The local side effects of the grass pollen allergoid was in the lower quartile compared with data from recently published studies, showing that as many as 26–86% of the patients receiving SCIT experience local reactions [12].

Systemic allergic reactions occurred in about 5% of our patients and were reported in more patients of the One Strength group (6.7 vs. 2.4%). Again, these data are in line with data published in adults [4, 12]. In our population, all systemic allergic reactions were classified as WAO Grade 1 reactions. All pediatric and adolescent patients reported TEAEs of mild or moderate intensity, and no TEAE was classified as severe. The frequency and the intensity of TEAEs were overall not considered a safety concern, and no change in the benefit risk profile of the medicinal product was regarded necessary.

Current asthma guidelines now recommend sublingual and/or subcutaneous AIT as an add-on therapy for asthma in adults and children based on results from recent clinical studies [6, 13]. However, uncontrolled asthma is still a contraindication for AIT, and patients with asthma are believed to be at higher risk for systemic side effects [14]. With respect to the subpopulation of asthmatic patients, our analyses revealed that there were no significant safety signals or other findings compared to the whole trial population. Nevertheless, our subgroup comprised only 29 children and 8 adolescents with AR and asthma. Even if our results are in line with recently collected data in adults [4], a larger population must be recruited to make a valid and evidence-based conclusion for asthmatic patients in this age-group.

A number of clinical studies have shown that functional IgG4 antibodies are induced by AIT [15]. We hypothesize that an accelerated dose schedule might offer the opportunity to gain clinical and immunological tolerance faster compared to standard dose escalation. Therefore, we assessed the change of specific IgG4 for *P. pratense* between the screening visit and the final visit as an exploratory end point. For children and adolescents, the mean amount of IgG4 against Timothy grass pollen increased significantly over time in both groups. The comparison between both groups revealed slightly higher IgG4 concentration in the One Strength group; however, this difference was not statistically significant.

Recently, Zissler et al. [16] reported data of an observational real-life, case-controlled, and long-term clinical cohort. They proposed 3 phases of the tolerogenic process during AIT and reported a correlation of the ratio of IL-10+ B-cells and Th17 cells during the early initiation phase to symptom improvement after 3 years of treatment. The hypothesis of a different tolerogenic effect might be supported by the clinical observation of a specific pattern of AEs in relation to the number of the individual injection. While the highest number of AEs in the high-dose escalation group occurred after the first and second injections in weeks 1 and 2, the number of AEs peaked in the standard dose escalation group in weeks 5 and 6. Hypothetically, these data might point toward a faster tolerance induction in the high-dose escalation group.

Beyond clinical trials, adherence to both subcutaneous and sublingual AIT is limited. Recently, Kiel et al. [2] showed that real-life persistence is better in subcutaneous AIT than in sublingual AIT in the Netherlands with 23 and 7% of the users that reached the optimal duration of treatment of 3 years, respectively. One potential barrier that might be opposed to a better adherence to AIT is the length of treatment. In this context, the advantage of a shortened AIT therapy is that administration of fewer injections is comfortable and more convenient for the patients having fewer visits in doctor's practice. In addition, less absenteeism from school or from leisure activities of children and adolescents is especially relevant for pediatric patients. For all patients in our trial, the mean treatment duration was 59.4 days in the One Strength group compared to 88.6 days in the Standard group.

An additional aspect of better adherence to AIT is the concept of "shared decision-making" [17]. Applied to AIT administration, health-care providers keep information on treatment options, that is, conventional versus accelerated updosing regimes of AIT and their potential benefits and harms. The patients' perspective addresses the current social situation and lifestyle preferences. Putting

these aspects together, this approach can lead to a shared decision-making, which might improve adherence and consecutively also clinical outcomes [17]. The accelerated updosing of AIT versus the conventional scheme of AIT might be a perfect example how health-care providers might initiate a process of shared decision-making. Future clinical trials should assess the impact of this tool on treatment adherence as well as treatment efficacy.

The strength of our clinical trial is that we recruited a good characterized clinical cohort of children and adolescents with AR with or without asthma and that we recorded the AEs comprehensively based on clearly defined clinical standards [18]. One weakness of our study is the open-label design, although blinding was not applicable with an acceptable amount of effort. Moreover, the efficacy of AIT was not measured in this study. Again, while measuring the clinical efficacy after 60 or 90 days might not be appropriate, prolonging our study over 1 or 2 years was not feasible. Finally, the number of recruited patients is quite small. Even if there were no new safety issues and no changes in the safety profile of the grass pollen allergoid, additional data in larger cohorts of children and adolescents are necessary for the confirmation of the overall good safety profile in our high-dose escalation group.

In conclusion, our results show that regardless of dosing schedule, AIT with grass pollen allergoid was safe and well-tolerated in children and adolescents with rhinitis or rhinoconjunctivitis with or without comorbid asthma. TEAEs were comparable between high-dose and standard dose escalation and predominantly local reactions. Systemic reactions were observed in about 5% in the One Strength group, but all of them were graded as WAO Grade 1. Altogether, the accelerated updosing scheme with a grass pollen allergoid offers an additional treatment option of AIT in children, adolescents, and adults.

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Statement of Ethics

The trial design was approved by the Ethics Committees of the University of Lübeck. The trial was conducted in accordance with the trial protocol, the International Conference on Harmonization guideline for Good Clinical Practice, applicable local regulations, and the Declaration of Helsinki. Patients willing to participate in the trial were asked to provide written informed consent after being given sufficient time to consider participation.

Conflict of Interest Statement

X. Bovermann has nothing to declare. I. Ricklefs has nothing to declare. C. Vogelberg has received a speaker honorarium or consultant fees from the following companies: Aimmune, ALK-Abelló, Allergopharma, AstraZeneca, Bencard Allergie, Boehringer Ingelheim, DBV Technologies, HAL, InfectoPharm, LETIPharma, Novartis Pharma, Sanofi-Aventis, and Stallergenes. L. Klimek reports grants and personal fees from Allergopharma, Germany, personal fees from MEDA, Sweden, grants and personal fees from Novartis, Switzerland, grants and personal fees from Allergopharma, Germany, grants and personal fees from Bionorica, Germany, personal fees from Boehringer Ingelheim, Germany, grants and personal fees from GSK, Great Britain, grants and personal fees from Lofarma, Italy, grants from Biomay, Austria, grants from HAL, The Netherlands, grants from LETIPharma, Spain, grants from Roxall, Germany, and grants from Bencard, Great Britain, outside the submitted work. M.V. Kopp has received a speaker honorarium or consultant fees from the following companies: ALK-Abelló, Allergopharma, Boehringer Ingelheim, Chiesi, Glaxo, InfectoPharm, Sanofi-Aventis, LETIPharma, Novartis Pharma, and Vertex.

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Author Contributions

X.B. enrolled the study population and was part of the writing team; I.R. was part of the writing team; C.V. analyzed the data and revised the manuscript; L.K. analyzed the data and revised the manuscript; M.V.K. designed the clinical trial, analyzed the data, and wrote the manuscript.

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